FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS

MENTHOL REPORT SUBCOMMITTEE

OF THE

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

(TPSAC)

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Rockville, Maryland

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C O N T E N T S

P R O C E E D I N G S

(8:08 a.m.)

Call to Order

DR. SAMET: Good morning. In this hush of expectation, I'll read the statement.

Good morning. I'm Jonathan Samet, chair of the Tobacco Products Scientific Advisory Committee. Good morning to everyone, and thank you for joining us. I want to make a few statements, and then we'll introduce the committee.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine

Act, we ask that the Advisory Committee members take care that their conversations about the topics at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks. Thank you.

Caryn?

Conflict of Interest Statement

MS. COHEN: The Food and Drug Administration is convening today's meeting of the Menthol Report Subcommittee of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members are special government employees and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts of interest when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a presentation and discussion of the timelines and structure of TPSAC's required report to the Secretary of Health and Human Services regarding the impact of the use of menthol in cigarettes on the public health.

This is a particular matters meeting, during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all committee members to disclose any public statements that they have made concerning the issues before the committee.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck and John Lauterbach and Mr. Arnold Hamm are participating in this meeting as non-voting industry representatives, acting on behalf of the interests of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers, respectively.

Their role at this meeting is to represent these industries in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company, Dr. Lauterbach is employed by Lauterbach & Associates, LLC, and Mr. Hamm is retired.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

I'd also like to remind you to please turn off your cell phones if you have not already done so, and I would like to identify FDA's press contacts, Jeffrey Ventura and Tesfa Alexander. And if you guys are here, please stand up. Thank you.

Introduction of Committee Members

DR. SAMET: Thank you. Let me proceed with asking the committee to introduce themselves.

Neal?

DR. BENOWITZ: Neal Benowitz, University of California San Francisco.

MS. DELEEUW: Karen DeLeeuw, Colorado Department of Public Health and Environment, and I'm the government representative.

DR. HATSUKAMI: Dorothy Hatsukami from the University of Minnesota.

DR. HENDERSON: Good morning. Patricia Nez Henderson, Black Hills Center for American Indian Health.

DR. CLANTON: Mark, Clanton representing pediatrics, public health, and oncology.

DR. ASHLEY: David Ashley, Center for

Tobacco Products.

DR. HUSTEN: Corinne Husten, Center for Tobacco Products.

DR. LAUTERBACH: John Lauterbach, Lauterbach & Associates, representing small business tobacco manufacturers.

DR. HECK: Dan Heck of the Lorillard Tobacco Company, representing the tobacco manufacturing industry.

MR. HAMM: Arnold Hamm, representing U.S. tobacco growers.

DR. SAMET: Let's see. Let me check.

Melanie, are you on the phone?

DR. WAKEFIELD: Yes. Melanie Wakefield, Cancer Council, Victoria, Australia.

DR. SAMET: Now it's evening, I think.

DR. WAKEFIELD: It's actually the middle of the night.

[Laughter.]

DR. SAMET: Oh, the middle of the night? Thank you for being with us.

DR. WAKEFIELD: You're welcome.

DR. SAMET: Hopefully this won't be too long.

Okay. Let's see.

Corinne?

Charge to the Committee

DR. HUSTEN: Good morning. As I think everyone is well aware right now, the charge to the TPSAC is to produce a report and recommendations on the impact of the use of menthol in cigarettes on the public health, including such use among children, African Americans, Hispanics, and other racial and ethnic minorities. And the report is due March 23rd of this year.

The subcommittee is divided up into writing groups that are developing chapters, and the writing groups will present to the TPSAC for discussion and deliberation of the findings and conclusions.

The topic of the meeting today is to discuss the report chapters, and the questions for the committee today are what feedback does the subcommittee have regarding the approach outlined

by each of the writing groups?

Any questions?

[No response.]

DR. SAMET: Thank you. So, as noted, our charge for today is really to have a discussion about the draft chapters that are evolving. Everyone will recall, of course, that we discussed chapters 1 and 2 yesterday.

I also want to note that March 23rd is not far off, and that we have had substantial input from the public. If there is to be any further submissions that the public would want us to review with the March meeting, the early March meeting ahead, those materials would need to be submitted by February 15th if they are written submissions. So just note that date, February 15th, for any written submissions that would be to be considered by the Menthol Subcommittee.

So what we're going to do today is spend time this morning on chapters 3, 4, 5, 6. Chapter 7, I think we will have only a conceptual discussion because that has not yet been drafted.

So we have slides for some of these, and not for others, to guide the discussion.

So I guess, Neal, we'll start with you and chapter 3.

Chapter 3 – Physiological Effects

DR. BENOWITZ: I do not have slides.

We discussed chapter 3 at the last meeting, so I thought what I would do is just go through the key questions we're looking at, the overview of what chapter 3 will include and some of our tentative conclusions.

The questions in this chapter really relate to many of the broader questions, but, specifically, we looked at questions of: Does menthol have cooling or anesthetic effects that reduce the harshness of tobacco smoke? Does menthol make low-tar, low-nicotine cigarettes more acceptable to smokers? Does menthol affect the metabolism of nicotine or tobacco-specific nitrosamines? And does menthol have the potential to increase the addictiveness of cigarette smoking? So those are the four questions that the menthol

chapter talks about.

This chapter really focuses on the physiology of menthol and the pharmacology. The first section reviews chemistry and sources. Then our second section summarizes what we've heard about the levels of menthol in cigarettes and how menthol is applied to cigarettes.

The third section discusses mechanisms of action, its effects on various receptors, on cold receptors, irritant receptors, chemosensory receptors. It talks about its activity in cooling, irritation, taste, aroma, et cetera.

The next section discusses interactions with nicotine, reviews data that menthol -- certain levels can reduce the harshness of nicotine. In other situations where nicotine levels are low, menthol can actually substitute and provide some of the impact that would otherwise be provided by nicotine. There is also data on desensitization and cross-desensitization between nicotine and menthol.

The next section, Effects of Menthol on

Nicotine Metabolism, there clearly are in vitro studies that show that menthol can affect nicotine metabolism. There's one human study showing a small effect. There are some issues that have been raised about whether the concentrations in in vitro studies can be achieved in human liver, but that's not really clear.

There is also the possibility, since there's a certain amount of pulmonary metabolism, nicotine and menthol can achieve substantial concentrations in the lungs, that some of the effects on nicotine metabolism could occur in the lung. The effects in the one human study that's been done are small.

In terms of effect on nitrosamine metabolism, there are studies, both in vitro and in vivo, suggesting that menthol reduces the glucuronidation of NNAL, which is a potential detoxification pathway. There are some studies that don't show effects, so there are studies both ways. But, certainly, if there is an effect, that is one way by which menthol could increase the toxicity or the carcinogenicity of cigarette smoke.

The final section deals with the sensory effects of menthol in cigarettes; so lower concentrations of menthol appears to be important to increase the smoothness of cigarette smoke, to reduce the harshness. In low-yield cigarettes, like I mentioned before, menthol can substitute for nicotine to increase the impact and make cigarettes more acceptable. And then for some cigarettes, where there are relatively high concentrations, menthol clearly has a very strong characterizing taste that some smokers like.

So that's a summary of what the chapter will discuss. The response to the questions; the first question would be that menthol does have cooling or anesthetic effects that can reduce the harshness of tobacco smoke. The second is, there are effects of menthol that can make low-tar, low-nicotine cigarettes more acceptable to smokers.

The third one is it looks like, based on the one human study, that there is some effect of menthol on nicotine metabolism, but it's small and it has unclear relevance in terms of nicotine

addiction. There are conflicting data about effects on nitrosamine metabolism. Certainly, if that effect is real, it could be important.

In terms of, does menthol have the potential to increase the addictiveness of tobacco, I think there certainly is strong biological plausibility. There's an unmistakable sensory experience with menthol cigarettes. The smoothing effects of menthol cigarettes could certainly make it easier for novice smokers to smoke cigarettes without the irritating effects. The fact that it makes low-yield cigarettes more acceptable could certainly make it easier for people to switch to low-yield cigarettes if they had health concerns perhaps instead of quitting.

There are effects of menthol to modulate nicotine effects which could play a role. Even though nicotine is the addictive principal, when you have something that alters nicotine effects, that could certainly play a role in addiction. And the strong sensory cues involved with menthol could be a strong condition association with effects of

nicotine, and that could also play a role in sustaining addiction.

So the bottom line here is there is certainly adequate biological plausibility to the idea that menthol makes cigarettes more addictive, and that's where we are.

DR. SAMET: Let me make a suggestion, since we don't have slides to organize this, that one way perhaps to discuss it and probably, particularly, to obtain input from our industry colleagues would be to go back perhaps and do section by section, remind everyone what was in those sections, and then come back to the conclusions.

Also, I think in terms of how we are putting the report together, if everyone will recall that in chapter 1, we set out seven questions related to individual smokers; 2 related to population, that we have discussed those questions, I think, going back two, three meetings and settled on those as key questions related to public health impact.

The four questions that Neal listed are particular to this chapter, but will be part of our

foundation of answering, addressing those seven plus two questions. And, in part, these relate to the biological foundation, the plausibility foundation, for addressing questions 1 to 7 for individuals and questions 1 and 2 for the population.

So these questions were, in essence, developed to give some structure to the chapter, and they represent key issues, then, that are a foundation for chapter 7, where we will be integrating across all the chapters to answer the questions.

So if everyone is in agreement about this way to proceed to give us a little bit of structure in our discussions, we'll go back to the first section.

Mark, please.

DR. CLANTON: Yes. I just want to remind the committee that I have sort of re-summarized those questions in chapter 7, so I'll put all that together on two slides so we can remember what those seven questions are as a group.

DR. SAMET: Thank you.

So just, Neal, let's go back and just do section by section. So your first was about menthol, as I recall.

DR. BENOWITZ: Yes. The first section was really just a brief overview of what menthol is, its chemistry, its structure, and the sources. And the source material came from tobacco industry's submissions, mostly.

DR. SAMET: Comments about this section? It's probably pretty straightforward.

[No response.]

DR. SAMET: Okay. Let's go on to the next.

DR. BENOWITZ: The second section is really just a survey of the levels of menthol in cigarettes and how menthol is applied. The application comes from tobacco industry documents.

Concentrations of menthol, some of them come from published articles. Some of the data will come from industry data. We will present menthol both in menthol per cigarette and menthol delivered in smoke. And we'll also talk about the issues of

menthol with low-yield cigarettes and the fact that when cigarettes are more highly ventilated, more menthol has to be added to the tobacco filler to have the same yield.

So these are the sort of issues that this section will discuss.

DR. SAMET: Okay. Questions? Comments?

[No response.]

DR. SAMET: Okay.

DR. BENOWITZ: The third, we'll talk about mechanisms of action, and this will be a summary of the various receptors on which menthol acts and the effects by those receptors; so the cooling receptors, the irritation receptors, chemosensory receptors, a summary, really, of just where menthol is thought to act.

DR. SAMET: Question, Dan?

DR. HECK: Yes. Just a suggestion. I'm sure this is being woven into the text. But on those topics of receptor effects, I think it'll be most valuable in the end if some of those effects that have been demonstrated in vitro and maybe in

animal models, we keep a careful track and documentation of those levels used relative to the levels we're able to develop in the cigarette smoke because, as you know, I'm sure there are different clusters of effects at low, intermediate and high levels. And it will be important, I think, to be mindful that the levels we might think about in cigarette smoke exposures should be, if possible, appropriately derived from those in vitro studies and not some of the extreme-level experimental studies.

DR. SAMET: And so I assume the concentration that would be relevant would really be the concentration in smoke, right, because these are direct effects in the upper airway.

DR. HECK: Yes, I think so. And, of course, the difficulty is, when you think about the interface with the biological system, what is the concentration locally, systemically, and depending on the effects of interest, both or either of those may be the most important.

I think everyone has had difficulty trying

to get at what is the level right at the tissue/smoke interface, let's say. There's probably various ways it can be estimated. But it's difficult to try to get at what that concentration might be. I know we've tried to do those calculations ourselves. It can be difficult.

DR. SAMET: Actually, just to interject, it seems like, if you're really interested in concentration at the air/liquid interface in the epithelium of the lung, and that volume is known, it would seem to me that those calculations might be done at least to get some ballpark. Perhaps they have not been done. So I think we're in agreement that they probably could be done. We're not going to do them, but --

DR. HECK: When it is possible to consider those sorts of things, I think it's important to try to do so in a documented fashion. I think various authors have approached that with exposures per unit surface area. There are estimates of the liquid volume in the respiratory tract. They're fairly frail numbers, I would say.

But certainly we have more information now on the levels in the smoke than we did a few years ago, and that would be a good starting point, I think, for reasonable calculations or estimations.

DR. SAMET: So this actually might be, perhaps, a research recommendation to think about.

DR. BENOWITZ: Any other comments?

[No response.]

DR. BENOWITZ: So the next section specifically deals with interactions with nicotine. This section overlaps a little bit with the last section. Certainly, at certain concentrations, menthol reduces the irritation, the perceived irritation, of nicotine. At other concentrations where nicotine levels are low, menthol can provide some of the irritation or impact to replace effects of nicotine.

Then there are issues of desensitization so that nicotine can reduce -- or that menthol can reduce or alter some of the effects of nicotine. So, basically, it's saying that menthol can really affect some of the sensory responses to nicotine.

I'll be summarizing that body of work.

DR. SAMET: Questions or comments here? Actually, Melanie, did you have something to say before?

DR. WAKEFIELD: I just had -- I'm not sure exactly where this goes. It might actually go in the first section. But I've been reading -- I've come across some material in my reading for the marketing section, which talks about individual differences in taste sensitivity to bitterness.

I was thinking that this could be something that could be relevant for chapter 3. I'm not sure whether you're already going to include that, Neal. But if not, I'd be happy to send along some references for you to evaluate.

DR. BENOWITZ: I would appreciate that. Thank you.

DR. SAMET: Dan?

DR. HECK: I might also add, Neal, I can provide some literature in that area. I'm not sure if we have it in hand already or not. But as it turns out, menthol taste threshold is actually a

fairly standard taste acuity test in the food technology area, so there is a bit of literature on menthol taste threshold.

Now, it's usually menthol in pure form, not in the milieu of smoke, so we have a little disconnect. But there is some literature there, and I could be pleased to provide any references I have on that for you.

DR. BENOWITZ: Yes. That would be great. Thanks.

DR. SAMET: Other questions or comments here?

[No response.]

DR. SAMET: Okay.

DR. BENOWITZ: Fifth section discusses the effects of menthol on nicotine and NNAL metabolism. Effects of nicotine, certainly in vitro, in liver microsomal systems, menthol can affect nicotine oxidation. The one human study that my laboratory did suggested that menthol cigarette smoking can reduce nicotine clearance by about 10 percent, affecting both oxidative pathways as well as

glucuronidation pathways.

There are questions here about extrapolating the in vitro studies to the in vivo studies because the concentrations of menthol in vitro would have to be reproduced in the liver to have the same effects. So, far as we know, menthol effects systemically are fairly low. In studies I've done and others, what we mostly see is menthol glucuronide in the blood. We don't measure very much menthol. So levels would be pretty low in the blood.

So it's not clear if menthol levels, when you smoke cigarettes, would be adequate in the liver to have the effects we see in vitro. However, about 10 percent of nicotine metabolism is thought to occur in the lung, and clearly -- and there are microsomes in the lung. And so there is the potential that menthol could have effects on nicotine metabolism in the lung, which could explain a small effect, even if we can't get levels in the liver. We don't know this for sure. It's just plausible.

I would also say that a number of studies that have looked at the hydroxycotinine to cotinine ratio, which is a phenotypic marker of nicotine oxidation via the enzyme CYP2A6, don't show effects; whether it means that there's no effect or if there's a 10 percent effect that some noisy measure could have been missed is not really clear.

The bottom line here, I think, is that nicotine does have -- or menthol does have the potential to affect nicotine metabolism. The effects are small and of unclear biological relevance.

Just on the second part of that is to look at NNAL metabolism. It is glucuronidated as part of its detoxification process, and there are some in vitro studies and some in vivo studies to suggest that glucuronidation is inhibited by menthol. Some studies do not find that effect. So we see conflicting studies about that.

So I don't think we can be definitive about that. We can just say that if that effect is real, it could be important in terms of carcinogenesis.

DR. SAMET: Mark?

DR. CLANTON: Neal, I apologize. I think I was supposed to go look this up. But we know that African Americans and certain people of Mediterranean descent do have differential metabolism of classes of drugs based on cytochromes and the P450 system.

Is there anything that you're aware of -- and if not, I'll go check the literature -- that talks about African Americans and metabolism of nicotine at the cytochrome level that is different than that of Caucasians?

DR. BENOWITZ: Yes. There's actually research from my group and from other groups that looks specifically at that. So African Americans have got a greater prevalence of CYP2A6 variants that are associated with slow metabolism. So on a study we did where we measured nicotine metabolism directly by infusing nicotine, we found, on average, African Americans mobilize nicotine 30 percent more slowly than do non-Hispanic whites, on average.

Also, there are isoforms of the UGT enzymes, which are involved in glucuronidation of both nicotine, cotinine, and also NNAL. And there's also evidence that African Americans have got a greater prevalence of slow-metabolizing variants there. And so there are a couple studies, at least, that show that the ratio of NNAL, glucuronidated NNAL, is lower in African Americans, which could be a potential risk factor for cancer in African Americans. So there clearly are differences.

DR. SAMET: Mark?

DR. CLANTON: So just one follow-up comment because I'm clearly not smart enough to put all that together. But if there is a way of looking at menthol as it relates to nicotine metabolism and then maybe synthesizing some of these other data relevant to African Americans, that would be very powerful.

DR. SAMET: I was actually going to say that it sounds to me like we're missing a section, in part given our charge. And what we're really

interested in is menthol by, in this case, racial/ethnic group as a surrogate for genotype interactions as they may influence nicotine metabolism, in fact.

I mean, it's a complicated topic, but that's actually what we want to address. And I guess the question is whether this would appropriately belong in chapter 3 or chapter 4, where we provide, at least, descriptive information about variation in patterns of menthol use across different groups.

But I think the topic is one that certainly is relevant to our charge, and I'm not sure we've put it in anywhere yet.

But Neal, do you think I phrased the issue correctly?

DR. BENOWITZ: Yes. There is actually material already in chapter 6.

DR. SAMET: That's true.

DR. BENOWITZ: But I think we should put some here as well in this section because I think those questions you ask are very important. We don't know anything about the interaction of

menthol with different enzyme variants, so I think that's a good point.

DR. SAMET: Yes. Dan?

DR. HECK: Yes. Mark, to your question and to Neal's summary, I think Neal gave a pretty good synopsis of what has become a large field of inquiry and research, that is, the pharmacogenetics in different ethnic groups with regard to nicotine and other drugs.

One thing I'd like to remind our committee, the total exposure study presentation we saw in July, and then another piece presented yesterday at the request of the committee, I think we have there probably one of the largest and best data sets where some of these inquiries on race-specific metabolic ratios and things like that are available in probably the largest study maybe that ever will be done on this topic.

So I want to be sure that the report does reflect that valuable information submission was made both in the raw data form, I understand, to the FDA and in the presentations given to date, and

indeed, in some of the published papers, like Wang et al., where this is discussed some in the paper.

So there were indeed racial differences apparent in that data set between blacks, whites, and I don't remember all the cuts they took in that, but it should be useful.

DR. BENOWITZ: Yes. We have included the total exposure study and the Wang study and your study as well.

DR. SAMET: Then I assume in the exposure study, there was no DNA set aside?

DR. HECK: I'm not recalling -- I'm not recalling whether there was or not for true genotyping, perhaps, in follow-up. I don't recall.

DR. SAMET: Okay. Anything else before we move? So I think we're at the conclusions now?

DR. BENOWITZ: Yes, final section.

DR. SAMET: Final section? Okay.

DR. BENOWITZ: The final section just brings together the effects of menthol sort of on the sensory response to nicotine. And here the

information mostly comes, or entirely, from tobacco company documents. So the data here indicate that in low concentrations, menthol has got a cooling effect and reduces the harshness and increases the smoothness of tobacco smoke.

In higher concentrations, it has an irritant effect, and so when nicotine levels are low in a cigarette, menthol can enhance the impact, and so can increase the impact and increase the acceptability of low-yield cigarettes; and that there are some people who clearly choose very strong characterizing taste cigarettes -- we talk about Kool and others like that -- where they just really like the menthol taste.

So I'll be summarizing some of the dose response issues for menthol, various sensory characteristics, and interactions with nicotine and tar.

DR. SAMET: Comments here? Dan?

DR. HECK: As to the statement that menthol may render low-tar, low-yielding cigarettes more acceptable, let you know -- I guess we've heard a

sense that that might be a bad thing, like does it provide an alternative to quitting. But let's not lose sight of the fact that there's the potential, at least, and we'll probably be discussing this in the years to come, for low-yield cigarettes to result in lower exposures to those smokers.

So an acceptable low-yield cigarette, or ultra-low-yield, as an alternative to a high-yielding cigarette, I think might have a net benefit even though we may not be able to measure that as quantitatively. So I just want to encourage us not to lose sight of that fact.

DR. BENOWITZ: Yes. So far, we don't have good evidence that the currently available low-yield cigarettes are less hazardous, but certainly that could be a possibility.

DR. SAMET: So do you want to go to the conclusions?

DR. BENOWITZ: So the conclusions, again, this first one was, does menthol have cooling anesthetic effects that reduce the harshness of tobacco smoke? I think it's pretty clear that it

does.

Does menthol make --

DR. SAMET: Why don't we do them one by one?

DR. BENOWITZ: Okay.

DR. SAMET: Comments on the first conclusion? And, again, remember, these are all sort of background to our answers to the overall conclusions. And you'll remember that we have, in chapter 2, set out how we're going to characterize strength of evidence.

That is really -- we're going to apply that framework to these overall, overarching questions. And here we have more specific questions that Neal is addressing with particular scientific data, so these will be, probably, conclusions couched in more general terms, I suspect.

DR. BENOWITZ: Yes. Yes.

DR. SAMET: So why don't you go on to the second one.

DR. BENOWITZ: So the second one is, does menthol make low-tar, low-nicotine cigarettes more acceptable to smokers? That looks likely from the

data that we've seen.

DR. SAMET: I guess we just had a little bit of discussion of that, but further discussion on this point?

[No response.]

DR. SAMET: Okay.

DR. BENOWITZ: The third one is, does menthol affect metabolism of nicotine or tobacco-specific nitrosamines? And the answer is, there is some evidence in humans that it affects nicotine metabolism. This is of uncertain relevance to addiction. There is some evidence, but conflicting, that nicotine can reduce glucuronidation of NNAL.

There's conflicting data. If that were the case, that would be a potential toxic effect, but I think it's hard to be definitive about how big that effect is.

DR. SAMET: Questions here? Comments?

DR. HECK: Just a comment on that NNAL glucuronidation, or let's say low glucuronidation, being a potential adverse situation. There are

some studies -- I'm not recalling the author offhand -- studies of different population groups who have inherently lower glucuronidation efficiency.

There have been -- the study I'm thinking of was in some of the written submissions and has looked at the lung cancer occurrence in those populations, and there really, I guess somewhat surprisingly, has not been good agreement with elevated lung cancer risk and the less efficient glucuronidation.

So it's probably a complex picture, as Neal alluded to. That was in I think a Pacific Islander population, but I'm not recalling exactly.

DR. BENOWITZ: Steve Hecht's work, I think, looked at this with the ratio and Pacific Islanders. I think so.

DR. HATSUKAMI: I think he did, but I'm not really quite sure.

DR. BENOWITZ: This, actually -- that part of it we're going to talk about in chapter 6. We're going to talk about biomarkers. But I think

that's a good point. We should make sure that we have that paper that looks at the ratio. I think that paper did show that there's a relationship between NNAL levels and cancer risk, but the ratio, I've got to go back and look at that.

DR. SAMET: So everyone thinks that is a paper by Steve Hecht? Probably. Sounds like it.

DR. HATSUKAMI: It sounds like him.

DR. BENOWITZ: So the last one is, is there a biological plausibility that menthol could enhance the addictiveness of tobacco? And I think that this is likely. And, again, the main effect is this unmistakable sensory experience, which we saw in enough animal studies. When you pair drug self-administration with sensory cues, animals self-administer faster and they self-administer longer, and they're more resistant to extinction. So I think, based on animal studies, there is that kind of plausibility.

In terms of initiation part of addiction, if menthol makes cigarette smoke smoother so that children who start smoking find smoking more

acceptable, that could enhance the addictiveness or at least the initiation part of it.

If you make cigarettes more acceptable at any level, whether they're low-tar or low-nicotine cigarettes or whatever, to smokers, flavor and acceptability is an important reason for people to keep on smoking, so that could certainly play a role.

Then we talked about some interactions with nicotine itself. And where it's not clear exactly how that would work, anything that modifies nicotine effects could certainly potentially modify nicotine addiction. And so I would say that there are enough data to say that there is a biological plausibility that menthol could enhance the addictiveness of cigarette smoking.

DR. SAMET: Yes. And I think, more appropriately, I think you had started by saying the addictiveness of tobacco. But I think as you phrased it at the end, it was of cigarette smoking --

DR. BENOWITZ: Yes. Cigarette smoking.

DR. SAMET: -- which I think is probably the right way to phrase the question.

So comments about this conclusion, where it's headed, and the rationale for the response? And actually, Melanie, just not to forget you, comments about this or anything else, if you're awake?

DR. WAKEFIELD: I'm okay at the moment.

DR. SAMET: So comments on this conclusion?

[No response.]

DR. SAMET: Okay. Chapter 3, done. We're going to go to chapter 4. How logical.

Chapter 4 – Patterns of Smoking

DR. HENDERSON: Good morning. First I want to apologize for my back being to the audience.

We presented this work last time, and we've added a couple more slides to further address a question that we had. The question that we're going to be addressing for this chapter is how it impacts population. The question is, does the availability of menthol cigarettes increase the prevalence of smoking in the population beyond the

anticipated prevalence if such cigarettes were not available, or within subgroups within the population?

So this is, of course, what we're basing everything on as we move forward. What we've done differently, or what we've added to this presentation or to this chapter, is to provide a description of the origin and early history of mentholated cigarettes. And, of course, the other two objectives are to explore the pattern of menthol cigarettes in U.S. populations, and whether it changes or not by race, ethnicity, gender, other social factors.

We've looked at many documents, including tobacco industry documents, peer-reviewed journals, presentations that were given by presenters here at their meetings, as well as presentations given to us by the public. And, so far, we have selected nine peer-reviewed journals that were going to be included, as well as presentations by several of the people that were here, as well as tobacco industry documents.

This is just a summary of the nine peer-reviewed journals that we're going to be presenting. And what we're going to be doing for this one particularly is really identifying in a table how menthol cigarettes are asked in these cross-sectional studies, and really understanding -- at least providing a really good description on the questions that were asked.

The only change that was made, or the only addition that was made, was we've added a publication that was recently published back in December by Hersey looking at youth patterns. And we're going to be providing a good explanation, or at least a description, of the National Youth Tobacco Survey.

MS. DELEEUW: I want to talk a little bit about what we're including in terms of the early history. These three bullets are identifying the sources of information related to the early history and origins of tobacco; the growth of menthols, 1933 to 1937, which is cited frequently in the literature. Another article that was presented at

a tobacco and nicotine research conference was a history of menthol cigarettes, and then we have also had some submissions from Altria.

The history and early origins have been referred to in several published articles, and these are three of them in particular that go through, basically, a summary of the history of menthol cigarettes that we'll be referencing.

Recently, we got some submissions which were basically reviews of the tobacco industry documents. And I think all three of these articles are on their way to publication, but certainly added a lot of additional information and summaries of the history of menthol cigarette use.

Basically, these are some of the main, I guess, conclusions in terms of looking at the literature. The origins and growth of menthol cigarettes are very well documented. The tobacco industry documents that are recently available contain an amazing amount of information on this topic. And, also, as you begin to look at the literature, you realize that the consumer research,

product development and marketing are inseparable from the growth of menthol cigarettes. So we'll see some things, I think, in chapter 5 that kind of weave some of this together.

Just in terms of some of the key points related to history, it's clear from the beginning that menthol cigarettes were marketed as a way to take -- either ease the hot, non-menthol cigarette consequences in terms of providing cooling history -- I mean, cooling sensations. The history, particularly the early history, is very interesting -- interactions between the development and marketing and growth of Kool, Salem, and Newport.

In 1956, after Kool had really dominated the market, but with only 2 or 3 percent share of the market, a lot of tobacco manufacturers jumped in to create and sell menthol cigarettes. And it's pretty clear that the patterns of menthol use among women, African Americans, and young adult smokers were present pretty early on in the development of menthol cigarettes.

Just one of the quotes that kind of summarizes the first point.

We're also looking at some other documents, in particular, looking after 1977, when the growth of menthol cigarettes study kind of concluded. These are some of the things that we've been looking at. The black smoker studies are very interesting because they're much more in-depth in terms of what was going on among African American smokers, and the amount of data and information that was collected in the black smoker studies was very extensive.

Here's one that is a black metropolitan smoker study, which was really looking, obviously, at blacks in urban areas compared to looking at them nationally. And what you notice in the documents is that a lot of the black smoker studies provide much more in-depth, and in some cases quite a bit different, data than what you see in the brand switching studies. And I think at this point we've decided probably to limit the inclusion of information from these studies just for the sake of

space, and also because I think the recent submissions on the industry documents summarize some of this.

DR. HENDERSON: This is information that was provided in our last meeting, basically looking at the share, cigarette share, for both non-menthol and menthol cigarettes.

Based on the information that we have gathered, we know that 1.1 million adolescents are now smoking menthol cigarettes here in the United States, ages between 12 and 17. This is data that was gathered between 2004 and 2008. And 18.1 million adult smokers are smoking menthol cigarettes, giving us a total of 19.2 million smokers who are smoking menthol cigarettes here in the United States.

This is just data that really highlights the disparities that are shown in different populations, where African Americans, Hispanic, and Native Hawaiian and Pacific Islanders are the three highest groups of smokers who smoke menthol cigarettes.

This is a trend looking at what has happened over the last -- during the four-year period from 2004 to 2008 between men and women, and what is happening with menthol cigarettes.

This is just a different way of looking at the slides in terms of what is happening in terms of menthol cigarettes among children and among adults.

Again, this is just looking at trends for adult smokers. And this is a quote that kind of just speaks to, I think, what the Act is asking us to look at, is children and what has happened over the past years, and how children have been targeted in many ways by the industry. And this is just something that was taken from the industry documents.

Again, to -- I mean, all these slides just really highlight the disparities that is shown in rates among -- this is among children. So these are middle school and high school students. And for African Americans and Asian Americans, they're the highest group of menthol smokers.

We're going to compare this data to what is happening with non-menthol smokers among youth. While the rates of smoking is going down in the general population, actually among the youth, among menthol smokers, it's very stable. Actually, it's increased over the past four years.

Again, the discrepancy or the disparities that is shown among different populations, and this is actually at sociodemographic factors. And again, blacks have the highest rates of smoking.

This is among men, and this is the trends looking at by race and ethnicity. And this is just basically showing what we've seen before, that blacks have the highest rates of menthol smoking.

This is among women. Basically the same patterns, and same thing.

We were asked to look at -- to see if we could find any journals looking at -- or any articles, anything that we could find, about the relationship between menthol cigarette smoking and mental illness, and we couldn't find anything; very few studies among minority and youth populations as

well. And these are just some of the limitations that are listed in looking at these peer-reviewed journals and other documents that were listed.

So, in conclusion, there is definitely -- if we were to go back to that question about, does the availability of menthol cigarettes increase the prevalence of smoking in the population beyond anticipated prevalence if such cigarettes were not available, there is strong evidence to support that, that particularly in African Americans, women, and children, there is definitely that issue.

DR. SAMET: Thank you.

Let me open up for discussion. Actually, let me ask first to Patricia and Karen that one of the issues that's been raised, I think, in our discussions with public commenters, is the question of the accuracy of classification of menthol cigarette use across the different surveys, the different questions used.

I think it's clear that there is always going to be some degree of misclassification. The

question of whether patterns of misclassification might be differential in some way, in some important way, and just how are you going to address this topic? I think this chapter does need to include up-front discussion on this issue, I know, and your drafts are considering it.

But do you want to comment a little bit on that?

Mark?

DR. CLANTON: This answer won't be entirely responsive to your question. But, number one, just based on the data and the ability to identify by class, we'll try to do that. But I want to make a counter-argument based on something we heard yesterday, which is, we actually have quite a bit of menthol use that's not classified. There are menthol cigarettes that are not predominately menthol brand, and there's menthol in cigarettes that are not predominately menthol brands at all.

So we're struggling in terms of this classification issue because we've got people smoking cigarettes with menthol in it, but they're

not classified in any particular way, per se, as a menthol cigarette.

So there's kind of a misclassification that goes in both directions. I'm not sure that we'll be able to deal with that perfectly accurately; but based on whatever surveys we have and where we can identify that, we'll try to identify misclassification as well as proper classification.

DR. HATSUKAMI: I would also think that just the fact that there may be consistency across the various national surveys, despite the fact that you have different classifications of menthol use, would be very important to point out.

DR. SAMET: I think -- go ahead, Karen.

MS. DELEEUW: Yes. I think one of the things, too, it will include a table that shows the questions from the different surveys so people can see exactly how they were asked.

DR. SAMET: I think one issue that you'll want to address, I mean, we know that these responses are subject to some degree of misclassification, as are roughly all responses. I

think a question for you is to lay out, could they possibly explain, for example, the high rates of reporting of menthol use in blacks versus other groups. Well, no. But could differential patterns over time, for example, in reporting, affect time trends that are more subtle? I think those are some of the kinds of questions and issues that you'll need to explore as you -- I think we just have to address this issue head-on. That's clear.

Again, there's the general issue of responses to surveys, and they've acknowledged some inaccuracies in reporting, both in smoking overall and then in menthol in particular. And, actually, in the surgeon general's report of 2006, we certainly tried to deal with -- 2004, rather -- some of the issues of reporting of active smoking. Again, there's references there that are available.

Let's see. Dan?

DR. HECK: I would just encourage, well, maybe a cautionary note for the authors here. We saw one document quoted referring to "younger smoker groups," something to that effect. I'm not

familiar with that particular document, but I would caution you, sometimes references in the literature analyzing those documents represent a phrase like that to mean adolescent smokers or youth or something like that.

If it's going to be a key point, you can usually do it with a click. But go to the primary source document and take a real look at that because as often -- I'd say more often than not in my own review like that -- I've seen reference to a young adult population, 35 and under, really not adolescent. So just be careful sometimes on some of those, and maybe take a glance at their source document and make sure it's solid.

DR. SAMET: John?

DR. LAUTERBACH: Going back to the slide marked, "References for Origins and Early History," a history of menthol cigarettes, "This Bud for You," Jack Reid was an employee of Lorillard Tobacco and not B&W. And that whole symposium volume, you can get new from North Carolina State University. It was not a B&W document. It might

have been bound in the B&W records, because I know they cleaned out my office. I had copies of all those things. But that's actually a Lorillard document.

DR. SAMET: And it's available in the Legacy documents if you don't want to buy it from the University Press, but maybe you should.

David?

DR. ASHLEY: I just have a question on the third slide from the end, "Other Special Populations," and you may have explained this as you're going through, but the second bullet, "There are very few studies on menthol cigarette smoking among minority and youth populations," do you mean minority youth populations, or are you saying there are very few studies on menthol cigarette smoking among minority populations and among youth populations?

DR. HENDERSON: Among minority and among youth.

DR. ASHLEY: So they're both minority and youth?

DR. HENDERSON: Right.

DR. HUSTEN: Although, actually, I was confused by that bullet as well because you had just presented all the survey data on minority and on youth, so it's a little bit confusing bullet.

DR. SAMET: I agree. So do you know what you mean or do you want to erase the bullet?

DR. HENDERSON: Yes. I was just going to say that it was minority youth, that we were -- because we were asked to begin to look at like different populations, the Asian population, the Hawaiian population --

DR. HUSTEN: So surveys?

DR. HENDERSON: -- yes, surveys. There's one or two out there but not enough to really give us a good understanding at the smaller subpopulations.

DR. HUSTEN: So, again, just to clarify, I think what I'm hearing you saying is there are few studies among certain minority youth populations.

DR. SAMET: And just on the severely mentally ill, in particular, I mean, this might be

flagged as an area for research for the future, a generally under study population, but one with a particularly unfortunate constellation of risk factors for disease.

Mark?

DR. CLANTON: And on the issue of menthol and mental illness, it may be obvious to the committee, but I want to make sure we understand why we wanted to look at that. There is a well -- if Jack were here, he would remind us there's well-established literature connecting nicotine addiction and addiction to other substances.

So we thought that it was important that in the mentally ill population and those who are addicted to other substances, we wanted to see if there was literature that described the interaction of menthol with either addiction and/or mental illness. So that's why that was there.

DR. SAMET: And, actually, I might draw your attention to the concern, I mean, following up on Mark's comments. For example, the HIV/AIDS

population and the IV drug users in which cigarette smoking -- in fact, probably the majority of HIV/AIDS-affected drug users smoke. And now there's concern with the advent of heart for chronic disease, longer term risks. There's literature, studies going on now on whether there is heightened lung cancer risk and risk for chronic obstructive pulmonary disease in these populations. Of course, there's a substantial proportion of African Americans among that group.

I don't know if there's any literature yet on types of products. There are certainly many cohort studies going on that might have that data. But, again, I think this fits into the research recommendations and would be very much in the sort of follow-up to what Mark proposed.

Let's see. Melanie? Do you want to say anything?

DR. WAKEFIELD: Yes. Thanks, Jon. Just a note here, really, that there probably will be a bit of overlap between this chapter and chapter 5 when we're talking about brand share because it's

very much related to marketing. But I don't think that's really a problem. I think it probably should appear in both chapters.

DR. SAMET: Anything else on chapter 4?

[No response.]

DR. SAMET: So today I'm going to be a kinder, gentler chair and propose that we take about a 10-minute break. The discussion of chapter 5 I think is likely to be lengthy. It's a substantially -- it's a long document. I'd just remind everyone not to discuss these materials during break. So let's reconvene at 9:30.

(Whereupon, a brief recess was taken.)

DR. SAMET: Let's reconvene. And we have chapters 5, 6, and 7, and then Dan is going to provide us with an informal overview of the report that he is shepherding along. And I think it would be useful to have a preview of that one.

So let's see. Dorothy, let's go to chapter 5. Are you going to do it all or is Melanie going to chime in, or how do you want to do this?

DR. HATSUKAMI: Melanie, are you still on the line? Did she get disconnected?

DR. WAKEFIELD: Yes. I'm here.

DR. HATSUKAMI: Yes. So I probably won't cover the marketing part, so you can go ahead and do that. But let me make some introductory comments first, and then I'll pass the baton to you.

DR. WAKEFIELD: Okay.

Chapter 5 – Initiation, Cessation & Marketing

DR. HATSUKAMI: So this is just to reiterate the process that we went to. We had a number of sources of documents, and at this point in time most of the sources that are relevant to this chapter have been identified. But we haven't yet vetted it for the quality. So I'm not going to make any firm conclusions from each of the areas that we're examining at this point in time.

As you can see, we have reviewed -- or we have identified peer-reviewed literature, and this is really the source of the predominant documents that we have been using. We also have looked at

papers written or commissioned by the FDA, the tobacco industry submissions, as well as any relevant scientifically-based public comments.

Now, we are having tables constructed, and they are to be completed the week of 2/14/11.

So this is the primary question for marketing, and that question is, does tobacco company marketing of menthol cigarettes increase the prevalence of smoking beyond the anticipated prevalence of such cigarettes if such cigarettes were not available, and also in subgroups within the population?

So, Melanie, do you want to take over here?

DR. WAKEFIELD: Sure. I will. So the next slide is just to remind you about some of the sub-questions.

DR. SAMET: Melanie, hang on one second. The slides just disappeared.

DR. HATSUKAMI: I'm sorry, Melanie. I think I pushed the wrong button.

DR. SAMET: And they're not reappearing. Oh, wait. No, here it is.

DR. HATSUKAMI: Here we are. All right.

DR. WAKEFIELD: So it should say, "Marketing, Branding, and Targeting"?

DR. HATSUKAMI: Yes.

DR. WAKEFIELD: Okay. So this is the first part of the section, and these are the sub-questions under that section.

I think what we've been finding is that quite a lot of these overlap. And we probably will do a little bit of reorganization to help the chapter flow a little better and not be so repetitive. A good example is that point 2, 3, and 4, there, what does the branding of menthol cigarettes promise; what is the content of the marketing efforts; and, what other messages are conveyed? I think it would be probably better to discuss all of those together rather than in separate sections.

The next slide is the set of questions that apply to the second section, and we're gradually working through those as well. And the next slide, which is called, "Marketing Section," this

basically shows you that we've got quite a lot of material for this overall section, and as Dorothy mentioned, most of the material is peer-reviewed papers. There are some reports. There are several tobacco industry document reviews, and there is some material from the various tobacco companies that have been submitted that we'll be using.

I've mentioned that many of that be references apply to more than one section. Another example is that when we're talking about the "four Ps" of marketing, one of them is place. Place also applies to the issue of target marketing as well, and target groups. So I think we've got a bit more work to do to sort of organize the writing of this section.

At the moment, where we're at is that we've abstracted the information from most of the material that we're likely to use, and we are in the process of commencing a quality appraisal, and Lisa Henriksen and I are sort of putting this section together.

So I don't think there's really much more to

say at this point about this particular section. The next section that Dorothy will talk about is huge, so I think more priority has been given to that at this point.

DR. SAMET: So, Dorothy, let me ask, do you think it will be best to -- do you want to go over everything and then come back, like we did with Neal? Or how would you like to approach talking about this, since there is so much? Give the overview and then come back section by section?

DR. HATSUKAMI: I think it's probably better to go section by section rather than to give the whole overview. So if we want to ask questions about marketing, we should do it here.

DR. SAMET: Okay. Then that's fine. And, actually, Melanie, I was going to ask if you could elaborate on the approach you're taking to evaluate the quality of the materials you're considering.

DR. WAKEFIELD: Well, we are requesting that some tables be prepared of all the materials that we're going to reference in the document, and that's going to have an overview of some of the

strengths and weaknesses of each of the studies. And I think that's quite important. So we're certainly going to be paying some consideration to that.

DR. SAMET: Just so there's clarity, some of the evidence tables are being assembled by -- I guess these are RTI.

DR. HATSUKAMI: RTI, yes.

DR. SAMET: -- RTI, contractors under the direction of the TPSAC writing group. And the strengths and limitations of the individual studies will be listed, but that will be based on the appraisal of the TPSAC writing group.

DR. WAKEFIELD: Right.

DR. SAMET: Okay. Other questions? As you can see, there's a substantial body of literature here. So let me open up for comments and discussion, then, on the marketing section.

Maybe, Dorothy, go back to the first slide here. Yes, this one. So these were the questions that are being addressed in this segment of the chapter. So let's start here with any questions.

[No response.]

DR. SAMET: Okay. Any questions on any of these few slides? The general approach has been set out.

[No response.]

DR. SAMET: Okay. Let's move on.

DR. HATSUKAMI: So the second primary question that this particular chapter is dealing with is the following: Does access or availability -- actually, we did change that -- to menthol cigarettes increase the likelihood of experimentation?

So what we've done is try to answer this question by looking at the various topics here. And so the first question that we asked is, what is the prevalence of menthol and non-menthol cigarette smoking among youth or experimenters by racial/ethnic groups currently, and then what has been the trend over time? And, so far, what we've found is that six out of the seven studies showed higher prevalence of smoking among youth and young adult smokers compared to older adult smokers.

We also looked at the literature among youth, and what we found is five of five studies showed higher prevalence among younger versus older adolescents, particularly among sub-populations, sub-ethnic/racial populations. And then one study found increasing trend of menthol use in adolescents. And based upon some of the public comments that we heard yesterday, we will be incorporating them. This is up to date prior to yesterday's discussion, so we will be adding the information that Dr. Hersey had presented as well.

Another question that we asked is, what type of menthol cigarettes do the adolescents tend to smoke, what are the popular brands, and then what has happened over time? And what we did is we identified five out of five studies, and one internal tobacco industry document review. It's a review that showed that adolescents preferred Newport cigarettes.

Then, according to yesterday's presentation, we found that some of the other menthol cigarette brands, such as the ones that are being marketed,

such as Camel and Marlboro, there has been an increase in terms of the adolescents using those cigarettes, whereas you see the prevalence, the trend, being flat for Newport cigarettes.

Here are some other questions that we asked. Is there a higher prevalence of menthol cigarette use among more recent youth or young adult smokers compared to more established youth or adult smokers? And what we found is that three of four studies showed higher prevalence among less-than-one-year smoker versus greater-than-one-year smoker. One industry submission questioned whether this trend that has been found is really due to -- it's a function of the switching definition that occurred, particularly in the NSDUH survey.

When you take a look at not duration of smoking but actually the number of cigarettes that are smoked, so looking at people that smoke from one to five, six to ten, so on and so forth, you really don't see any differences in terms of the prevalence of menthol smoking according to the amount of smoking.

Another question that we try to answer is, is there evidence to show that there is an earlier age of initiation among menthol smokers compared to non-menthol smokers? And eight out of nine studies show no difference in age of initiation. One study showed no difference in adults, but earlier initiation among youth; and one internal tobacco document study reported no differences.

Another question is, what is the pattern of switching among this population? What is the extent to which smokers who initiated smoking with menthol cigarettes switch to non-menthol cigarettes, and what is the extent to which non-menthol smokers switch to menthol cigarettes?

We found six studies, one internal industry document review study. And what we found is that there are some mixed results. There is a low -- we found that there were low rates of switching between cigarettes. But one study did show that youth who initiated smoking with menthol who switched to non-menthol were more likely to transition to increased smoking and dependence than

those who initiated with non-menthol cigarettes.

So here's, finally, does menthol make cigarettes more tolerable for the inexperienced smoker, thereby increasing the likelihood of experimentation? We found one study that showed no effects among the menthol initiators, but four internal tobacco document studies support the idea that menthol cigarettes make smoking more tolerable to the inexperienced smoker. So that is concordant with some of the results that Neal has come up to show biological plausibility that this might occur.

The other questions, what are some of the other influences for the use of menthol cigarettes? We're still looking into that. And do beliefs about menthol among peer groups or parents affect the initiation of smoking menthol cigarettes? And we didn't identify any studies.

So I think, in summary, what we have found is that there is a high prevalence -- we do see an age gradient in terms of the use of menthol cigarettes. And we are really concerned about the increasing trend of menthol cigarette use among

adolescents. And what we observed is even though -- actually, the adolescent smoking has plateaued, but there had been a decrease in adolescent smoking.

In spite of that, we see that the slope of the decrease is a lot less among the non-menthol adolescent smokers compared to the menthol adolescent smokers. So we are a bit concerned about that.

So that are the conclusions or some of the thoughts that we have at this point in time. And, again, we haven't vetted the studies yet for quality, and so that might change it a little bit by the time we finish this report.

So I'll stop with that, if people have any questions.

DR. SAMET: Questions? One issue you might want to just discuss a little bit, and I think it's certainly one we heard about yesterday in the Covance presentation, among others, the interpretation of some of the cross-sectional data on age trends and how far we can take those

interpretations around a higher prevalence of menthol use at younger ages, and whether one can interpret the -- how the cross-sectional dropoff is interpreted.

Do you want to --

DR. HATSUKAMI: Ideally, we would have had a longitudinal cohort study. That would have been the ideal situation. But we don't have that at this point in time. But I think the cross-sectional study, the time period is so short, and still we these trends, that the issue of cohort effect is probably not as of great concern as if you were taking a look at from 1990s to 2009.

So it's not the ideal study, but I think that we can certainly make some conclusions.

DR. SAMET: I think certainly we'll want to address this potential concern --

DR. HATSUKAMI: Right. Yes, we will.

DR. SAMET: -- which has been --

Other comments?

[No response.]

DR. SAMET: Melanie, do you want to weigh in

here at all?

DR. WAKEFIELD: I'm fine, thanks.

DR. SAMET: Okay. Then I guess the next section.

DR. HATSUKAMI: So this is the next question, does access -- I'm sorry -- availability to menthol cigarettes increase the likelihood of becoming addicted? Does inclusion of menthol in cigarettes increase the degree of addiction to the smoker?

So what we did is we asked several questions related to this, and one of the questions is, what is the prevalence of -- oops, sorry -- is there evidence to show that menthol alters levels in PK of nicotine to make menthol cigarettes more addictive?

I think, based upon what Neal had talked about today, we're just going to punt that to his section. And it seems like some of the results are pretty limited to support that menthol might alter nicotine metabolism. And if it does, it may be at levels that are insignificant related to how it

might affect addiction.

The second question that we tried to address is, is there evidence through animal and human studies to show that menthol enhances the abuse liability of nicotine or menthol cigarettes?

Unfortunately, there are no specific studies of abuse liability that have been identified. But there were a couple of studies looking at economics, actually, that might suggest that, in fact, menthol cigarettes do have higher abuse liability.

There was one study that showed that non-menthol cigarettes were less of a substitute for menthol cigarettes if the price is increased on menthol cigarettes than vice versa. And, also, they found more menthol smoking in states that have stronger laws restricting smoking, essentially. So those might be indications that there might be higher abuse liability with menthol cigarettes.

The other study showed that as price increases and smoking decreases, menthol smokers tend to compensate more aggressively than non-

menthol smokers by switching to a higher-tar or higher-nicotine cigarette. Again, that's very suggestive that there might be higher abuse liability with the menthol cigarettes.

The other question here is, is there evidence to show that youth experimenters -- that is, those who are smoking less than 100 cigarettes in the lifetime -- respond to menthol cigarettes differently compared to non-menthol smokers, and what might be moderating factors.

Unfortunately, we didn't really find any studies that showed how experimenters might respond to these cigarettes differently that might actually lead to an escalation in terms of nicotine addiction; so no direct studies that have been conducted in that particular area.

Do smokers who experiment with menthol compared to non-menthol cigarettes, are they more likely to become regular smokers? Are they more likely to become addicted smokers? So, for example, are those who begin smoking menthol more likely to continue smoking than those who are

initiating with non-menthol cigarettes?

So I think one study did -- it was a good study. It was the Nonmacher (ph) study, found that youth who initiated smoking with menthol were more likely to transition to increased smoking and possibly dependence. So we do have one study that strongly supports that.

The other question, do menthol smokers experience a more rapid trajectory toward regular smoking or addiction compared to non-menthol smokers? And what we found is that there was one internal tobacco document study, so a review, and one adult smoking study that reported faster transition from initiation to established smoking with menthol cigarettes. But, again, this area is a little bit limited and really cries out for more data analysis or research.

Do menthol compared to non-menthol cigarette initiators tend to be a population more vulnerable to addiction? And I think I said that it's going to be addressed in chapter 4. And it seems like you folks didn't really find any studies to suggest

that, or there are no studies, period.

Let's see. So the next section, the next set of questions that we asked, is, menthol cigarette versus non-menthol cigarette smokers, do they differ in the extent of addiction, and that would be measured by cigarettes per day, exposure to nicotine such as levels of cotinine -- measures of nicotine such as nicotine equivalents, levels of cotinine, cotinine per cigarette.

Actually, this is a section that -- I think it may be covered in chapter 6, so I guess I won't really go through it. But we really didn't see a lot of evidence to support that menthol cigarette smokers, even controlled for race and ethnicity, that there were really any differences in terms of these biomarkers of exposure or cigarettes per day.

Now, another way to measure extent of addiction is looking at the FTND, time to first cigarette, waking up in the middle of the night, which is not a measure that has been used widely, but seems to be related to cessation rates. So it can become a more validated measure in the future,

and then withdrawal symptoms.

So among the adults, if you take a look at the studies that have looked at FTND, we found that five out of six studies found no differences. Time to first cigarette, seven studies showed shorter time to first cigarettes, especially in specific populations of menthol smokers. One showed a trend. Nine studies showed no differences.

Waking up in the middle of the night, two studies showed positive relationship with menthol smoking. Other dependence measures, four studies showed no consistent effect, withdrawal symptoms; one study showed no difference.

The one area -- we did take a look at adolescents, then, to differentiate them from the adults. And what we did find in that particular area is that eight out of the nine studies showed higher dependence, higher indicators of dependence, among youth who smoke menthol cigarettes versus non-menthol cigarettes.

So that's the end of that story. So, basically, what we find is that the areas that are

of particular concern to us is the fact that among initiators in youth, that there is an escalation towards heavier smoking and possibly dependence if they start initiating with menthol cigarettes versus non-menthol cigarettes.

We're also concerned about the fact that adolescents do seem to be more dependent if they're menthol smokers versus non-menthol smokers. But among the adult population, you don't see, really, any differences in terms of extent of addiction.

DR. SAMET: Okay. You covered a lot of ground. Thank you. And let me open this up for questions and comment.

[No response.]

DR. SAMET: Melanie, comments?

DR. WAKEFIELD: No. I don't have anything further, Jon.

DR. SAMET: Okay. Dorothy, anything else you want to weigh in on here?

DR. HATSUKAMI: No. I think that's it. I guess I stunned people to silence.

[Laughter.]

DR. SAMET: Yes. You overwhelmed us.

DR. HATSUKAMI: All right. So here's the primary question for -- this is the last question. Are smokers of menthol cigarettes less likely to quit successfully than smokers of non-menthol cigarettes? So we looked at the likelihood of cessation by mentholation, and also we looked at any mediators that might affect cessation among menthol smokers.

So here's the first question. What is the evidence that menthol cigarettes decrease cessation in general by age and by racial/ethnic groups? We identified 25 adult smoker studies. We didn't identify any adolescent studies that we thought were qualified enough to include in this report.

Among the adult smoker studies, 11 studies showed no effect. These included two population surveys, four longitudinal cohort studies, and five treatment studies. So there is a lot of variety in the type of studies we looked at.

There's two studies, actually, that showed better cessation among the individuals that smoked

menthol cigarettes. These were surveys, actually. And then ten showed poor cessation, and they included four population surveys, one longitudinal cohort, and five clinical trials.

I have to say that these studies varied, so we're currently vetting them. For example, there were some studies that looked at selective population, like female prisoners, and so that really minimizes the generalizability of that particular study. Other studies looked at a VA population; tended to be older smokers, again limiting the generalizability of that study. So we're going to be vetting those studies for that. There are some studies that had overlapping pool of subjects, so we're going to have to take a look at that more carefully.

But, in general, the studies, in terms of treatment outcome, it doesn't seem to be an effect of mentholation, but we're trying to drill down a little bit more, and there's some suggestion that -- I'm sorry; I should have said menthol cigarettes and not mentholation. But there is some

suggestion that potentially, a non-white population might in fact experience poor treatment outcome than a white population. But I don't want to make any firm conclusions on that at this point in time until I really study the quality of these studies.

Some of the population studies, I must say, were -- actually, the quality was better among those that showed poorer cessation than the ones -- the survey studies, that didn't show any kind of effect of menthol cigarettes. But, again, I don't want to make any firm conclusions.

One interesting finding that we discovered is that it appears that menthol cigarette smokers may in fact not respond as well to pharmacological treatments compared to non-menthol smokers. So we identified three, possibly four, studies that looked at this particular issue, and three of the studies, and one other suggested that, for example, menthol smokers who are treated with NRT don't respond as well to that treatment.

What's interesting in these studies is that if you take a look at the placebo group, you really

didn't see any differences in terms of treatment responses; only when you took a look at the group that was given medications where you find a poor outcome among this population.

So in terms of mediators of cessation, is there any evidence to show sensory effects for menthol might in fact reduce cessation, there were no empirical studies that were identified. And, actually, there were more than one internal industry document, papers -- it was more than one. And certainly in those papers it was suggested that, in fact, some of the sensory effects from menthol might reduce the probability of cessation.

So I think at this point in time, again, very preliminary conclusions. We're going to still take a look at the quality of the studies. But it may be that the non-white population might be at less likelihood of quitting if they are menthol smokers. They may not be as responsive to treatment.

DR. SAMET: So just as a reminder, this chapter really cuts at a number of our questions at

the individual level, and then also at the population level. Of course, it will be joined -- the findings here will be joined with the other chapters as we answer those questions. But there is I think results here that are very important as we think about our conclusion.

DR. HATSUKAMI: Right. Right.

DR. SAMET: So let me open up here for discussion. Dan?

DR. HECK: Not so much a specific question for Dorothy; perhaps a question for the whole group. I'm just struck by the large numbers of studies mentioned here. And just wondering, these resource papers mentioned here, are they all in either the NCI bibliography or in the subsequent bibliographies that were provided to the public?

DR. HATSUKAMI: Yes. All these documents were provided to the public. So there was a lot of secondary analysis of data, for example, that was provided to the FDA at the last meeting. And so it's based upon those documents that should be on the website.

DR. SAMET: Actually, it might be useful both for you and Melanie to provide a little more information, if you want to talk about it now or in the document, about the strategies by which these documents were -- the various sources of evidence were identified that you reviewed; it came from the peer-reviewed literature, your own searches, et cetera.

DR. HATSUKAMI: Right. Right. So, yes, we looked at the bibliography source that was provided to us by the NCI documents. All the public comment -- or all the documents that were commissioned by the FDA, the white papers that were commissioned with UCSF, we reviewed. Any of the secondary analysis that were -- I guess there was an RFA that went out, I believe, that was funded by the FDA. All those secondary analyses were reviewed; any new documents that we received or were discussed in public comments, such as the one that Hersey and some of the other folks at RTI had presented yesterday, all those documents that are out in public, we reviewed. And any of the

information that was provided by the tobacco industry was also -- they were also examined.

DR. SAMET: Corinne?

DR. HUSTEN: Yes. Just to clarify the process a little bit, we had asked the writing groups that if they identified articles that weren't already available to the public as they were working on their chapters, to give those. And they are all included in the bibliography.

So whatever the writing groups identified as sources that may not have been out there previously, as we've gotten them, we've put them into the background bibliography for each meeting.

DR. SAMET: Other questions? Comments? Melanie, anything from you?

DR. WAKEFIELD: Yes. Really, just to add to what's been said, certainly in the marketing section, we've drawn quite a bit from the NCI monograph, which had four chapters on tobacco marketing. There are some other articles that we identified from our own searches which we've given to FDA, which I assume have been listed now in

what's been sent out. So, yes.

DR. SAMET: Good. All right. We're going to leave chapter 5, and wait to see it in its full glory and length.

So chapter 6. Maybe now you could actually pass the changer towards Neal and myself.

This is a joint work in progress, and Neal, why don't you go ahead?

Chapter 6 – Risk Factors

DR. BENOWITZ: So the focus of this chapter is the effects of menthol on disease risks of smoking. And there are four sections, the effects on menthol on topography, biomarkers, toxicology, and epidemiology.

This addresses questions 6 and 7. Question 6 was that, do biomarker studies indicate that smokers of menthol cigarettes receive greater doses of harmful agents per cigarette smoked in comparison with smokers of non-menthol cigarettes? And number 7 is whether smokers of menthol cigarettes have an increased risk for diseases caused by smoking in comparison with smokers of

non-menthol cigarettes.

So, as I said, these are the four topics that are covered. Search strategy -- basically, literature searches, FDA white papers, and public submissions were all examined here. This is a relatively circumscribed database, so I think we have pretty much everything that's available.

For the topography -- and by topography, this is really meant to look at smoking behavior. So is there an effect of menthol on how a person smokes a cigarette? And within this section, we've also included biomarker studies from individual cigarettes. So one could look at the boost of nicotine, which means the increase in nicotine from before to after smoking a cigarette, or the carbon monoxide boost.

So 11 studies were identified, and I actually should say that we also in this section talk a little bit about the race confounders, because many of these studies, especially the topography studies, are small. And when you have a small study, and most of the menthol smokers are

African American and most of the non-menthol are whites, there's a lot of potential confounding since work from my laboratory and others suggests that African Americans smoke cigarettes differently than whites in general. They smoke fewer cigarettes per day. They take, on average, more smoke per cigarette, at least in some of our studies. So that's a problem with these because when you have a small end, it's very difficult to disentangle the confounding.

So eight studies looked at the effects of menthol, the number of puffs or puff volume. Five studies reported carbon monoxide levels. I think one or two studies looked at nicotine levels. The results varied from study to study. The designs varied, too. So some found increased puffing, some decreased, some no changes. On balance, there was no consistent effect of menthol, at least so far as we can control it with the race confounding on topography.

On biomarker studies --

DR. SAMET: Do you want to stop and see

if --

DR. BENOWITZ: Oh, okay. Let me just see if there are any comments.

DR. SAMET: Yes. So let's do this section by section.

So comments on the topography?

DR. HECK: Just a comment more than a question, I think. I'm not sure, among the studies reviewed here, some of these newer studies on the "yield in use" or "mouth-level exposure" or "butt analysis," by various terms, were considered. I know the CDC has done some work in this area as well as some of the industry groups. But it has some elements of a biomarker study and some elements of topography, basically measuring -- taking account of what emerges from the tip of the cigarette into the mouth of the smoker, getting close to internal exposure.

I think the study of Nelson et al., and some of St. Charles et al., in recent years -- a few of those had some menthol comparisons in them. So I just wasn't sure those were caught in this survey,

but I think those might be useful to look at. And the CDC work on that, I don't recall that there was any separate menthol analysis, but –

There isn't? Okay.

But, anyway, I just wanted to bring that up.

DR. BENOWITZ: Thanks. Those have not been included, and I think that it would be good if we could get those papers to include them.

DR. HECK: Yes. I can certainly provide those to the TPSAC mailbox or whatever would be the most appropriate way.

DR. SAMET: John?

DR. LAUTERBACH: I believe, Caryn, I sent those to you, at least the St. Charles ones, did I not?

MS. COHEN: Yes. They went out.

DR. SAMET: We'll find them. Sometimes they get buried.

Dan and Neal, maybe the question -- and this came up a little bit yesterday -- just terminology. Mouth-level exposure -- and again, I'm stuck in a different framework of thinking about what exposure

is; mouth-level potential dose, what terms -- I mean, just so we in a sense have a harmony of terms in terms that those who work in the tobacco field will recognize.

Again, I've been thinking about, at least in the National Research Council biomarker reports going back into the '80s, the conceptualization has always been, of course, concentration exposure, concentration times time; and then the variance dose metrics, potential dose, which to me would be the amount of stuff, let's say, in a puff or in the number of puffs inhaled, the actual intake, the biologically effective dose, dose to target sales.

David, you might weigh in here, too. But it seems like there's a lot of mixed use of terms across different sectors. And if nothing else, and maybe, in fact, in the introduction of this chapter or somewhere back earlier, we should say what we mean.

So does anybody have any thoughts about where terminology fits? And a lot of this turns out to be in the hands of individual authors, I

think.

DR. HECK: Yes. I think I share your observation that there isn't consistency at this point. I know some of the groups use the term "mouth-level exposure" and "yield in use" or "cigarette butt analysis." I'm not sure which of those the CDC may have used in their work.

But, basically, you look at the expended cigarette butt smoked by a real smoker in his or her real way, and once calibrated for each brand with a smoking machine across the spectrum of smoking intensities, you can get really good correlation with some biomarkers measures in some of the validation work that's underway right now with CORESTA, the biomarkers and smoking behavior subgroups.

Quite a good estimate of what at least exited in the cigarette in the smoker's mouth, there's some mouth spill. But the correlation with some biomarkers such as salivary cotinine, maybe nicotine metabolites as well, has been above .9. So it's actually pretty close to what estimates you

can get from the more cumbersome biomarkers measurement in urine or whatnot.

So, granted, the method is kind of emerging and not fully standardized yet. But I think it does show promise, and that there's -- at least a few of those studies have broken out some menthol versus non-menthol comparisons.

DR. SAMET: Let me get David to weigh in, and then I think just some discussion about whether in this chapter at the start, when we talk about topography and these different metrics, we maybe say, here's what we're going to use, and when we say dose, this is also equivalent to what people refer to as blank. I think we just -- maybe, David, weigh in. Help us.

DR. ASHLEY: Yes. I understand your question here, and it's actually a very good question. I know at CDC what we've used is the term "mouth-level exposure" for what Dan's talking about, exposure is probably not the right term because we don't have a time. It's not a time thing. So probably "mouth-level dose" may be more

appropriate because it is how much you're taking in, the dose you're getting from a cigarette.

I think it would be very worthwhile to define what we're talking about because it is important to carry over and maybe even reference what words other people have used, like "yield in use," so those things are all clumped together and then one terminology is used throughout the chapter.

DR. HECK: And maybe it's apparent from our description here, but the nice thing about this approach, it's relatively expedient compared to biofluid collection or something, and you can capture all the elements of smoking behavior; puff number, puff intensity, puff volume, vent blocking to the extent that occurs. All that's captured in that signature of what is retained in the cigarette butt by the real smoker. I think moving forward, I think the method will show some real promise for some insight.

DR. BENOWITZ: Of course, one problem with it is that there is a lot of dilution of smoke

after it gets into the mouth with outside air, and the percentage mixture varies a lot from person to person. So I think it still is not as good as a systemic biomarker.

DR. HECK: I wouldn't disagree. But there is some mouth spill during that second stage of the inhalation, but it's pretty close. And it's easier to do a larger study, and we've to date had some pretty good correlation with those more definitive biomarkers.

DR. ASHLEY: I think Dan mentioned it already, but the other thing you don't get is the difference between taking a puff and inhaling. You get what comes into the mouth. You don't get whether that person actually pulled into the lungs or how much they pulled into the lungs. So there are some -- I mean, it's not perfect, but it's a reasonable measure.

DR. SAMET: Okay, Neal. Another tough assignment for you, but I think this will be important just to harmonize a bit.

DR. BENOWITZ: So the second part is looking

at systemic biomarkers. So these are studies where you measure constituents of tobacco smoke in biological fluids. The main ones that have been looked at have been nicotine biomarkers, and this is generally blood nicotine; blood cotinine -- actually, cotinine more so, blood and plasma; urine cotinine; urine nicotine equivalence, which is really the sum of major metabolites of nicotine; NNAL, which is a metabolite of the tobacco-specific nitrosamine carcinogen NNK; carboxyhemoglobin, which is a measure of carbon monoxide exposure; polycyclic aromatic hydrocarbon metabolites, that's another class of carcinogens.

There are also some studies that have looked at metabolites of volatile organic compounds like acrolein or 1,3-butadiene or benzene that have been looked at. Some have also looked at biomarkers of cardiovascular disease, inflammatory markers, endothelial function markers, oxidation markers, et cetera.

So there have been a number of studies of markers. Eight studies have been cross-sectional

studies, looking at these various markers. One study from my laboratory looked at a specific question about whether there's a quantitative relationship between menthol exposure and exposure to biomarkers. That study actually looked at urine menthol levels as an indicator of menthol dose versus biomarkers.

The bottom line between these studies, there's some variation but there does not seem to be a strong signal between menthol cigarette smoking when controlled within race and exposure to biomarkers.

One caveat in both the topography studies and the cross-sectional studies, which I have mentioned at prior meetings, is that most of these studies are done in people who are regular smokers of many cigarettes per day. The total exposure study might be one exception, but most other studies are people smoking ten or more cigarettes per day.

One question about menthol cigarettes is whether, if you are reducing the number of

cigarettes, does menthol allow you to inhale a cigarette more deeply because there's less irritation and take in more per cigarette. We don't have any good topography data on people who are occasional smokers -- or not occasional, but light smokers in terms of, say, five or ten or fewer per day.

We heard something yesterday in the total exposure study about fewer than ten cigarettes per day. I think that was useful. But there's still a gap. We still don't have a good dose response in terms of the effects of menthol in the continuum below ten cigarettes per day. And so that's a gap, a research need for the future.

That summarizes, I think, this section.

DR. SAMET: Questions? Comments?

[No response.]

DR. BENOWITZ: So now it's you.

DR. SAMET: It's me?

Well, here's the toxicology section.

[Laughter.]

DR. SAMET: I'll just say that I think my

attention has been elsewhere. And just in terms of gathering the literature and looking at sources, in fact, there are a number. There was a review that I think was presented at our first or second meeting, an overview that Alison (ph) did. Dan, in fact, in his review of, what, two years ago now, cuts on a number of toxicology papers.

I've done a literature search; I have just not embarked on this.

Questions or comments, or volunteers?

[Laughter.]

DR. SAMET: And then the epidemiology. And actually, the epidemiological studies, I think, have been discussed. The public commenters have presented and summarized the literature. There's, again, a relatively constrained body of epidemiological studies. And, in a way, I'm actually surprised, given how much work has been directed at tobacco and health and disease, that there are so few studies. There are not that many, and I think that universe has been well documented. I think its strengths and weaknesses have been laid

out in these public meetings, and we will be, again, summarizing those same studies and evaluating them.

I think I would just note that they span a relatively long period of time over which they were conducted. And that, I think, constrains somewhat their interpretation. And, again, if you think about some of the data we are aware of on some of the time course of penetration of menthol into various markets, we don't have the window of looking at people who have -- large numbers of people who have smoked these types of products for a long time.

But the data are laid out there. And I think we've seen, even, as recently as yesterday in one of the presentations, what the summary -- what the relative risks look like. And we know that those are roughly clustered around unity, comparing the relative risk for disease in smokers of menthol compared to non-menthol cigarettes.

So I don't think this section is going to yield any surprises. So let me see if there are

any comments here. And, again, at this point, the data have been assembled into a table and we've looked at the evaluation of these studies.

Dan?

DR. HECK: Just a passing comment, Mr. Chairman. I saw in the chapter 1 and 2 draft, I think not unreasonable inclusion/exclusion criteria, and that things available only in abstract form would probably not receive a lot of consideration.

As you're aware, there is one epi study, this Yukel (ph) and colleagues, that I've been able to obtain only in abstract form from a biometrical meeting in Germany. It's interesting, at least, because it's the only population with a menthol epi from outside the U.S. that I'm aware of. And the numbers are relatively small, and it was a study of German menthol versus non-menthol smokers.

But I think the outcome of the study, as we can understand from the abstract, looks a lot like the U.S. epi. So I just thought I'd mention that, that there is menthol presence elsewhere in the

world. But this is the only study I'm aware of where that's been broken out in a risk comparison.

DR. SAMET: Thank you, and worth a mention.

Okay. That's chapter 6.

Anything, Melanie?

[No response.]

DR. SAMET: Maybe Melanie went to sleep.

DR. WAKEFIELD: No. I had the mute on. Actually, I'm still awake. I don't have anything more. Sorry.

DR. SAMET: Okay. That's all right.

Let's go to chapter 7.

Chapter 7 – Public Health Impact

DR. CLANTON: All right. I'm going to make a conceptual comment about the purpose of chapter 7, then we're going to just remind you that a good part of the first set of slides represents placeholders for information and conclusions that will be pulled forward from previous chapters. And, finally, there's at least one section that will look at contraband, and I'll explain why we're looking at it, and then explain some of the topical

headings that were derived from testimony from the last TPSAC meeting.

So, first of all, it is worthwhile to remind everybody that the purpose of the entire report is to describe the impact of use of menthol cigarettes on the general public health, with special attention to groups such as children, African Americans, Hispanics, and other racial and ethnic minorities.

It is in chapter 7 where we'll attempt to, as specifically as possible, address this question or these questions around the health and public health impact on these particular groups and in general.

This is simply the section of the law that causes us to examine a set of questions. You were reminded earlier by our chair that there are seven specific questions that we are required to address. And, once again, with respect to the placeholder function of chapter 7, it will be in chapter 7 that we attempt to answer those seven specific questions.

So I do want to just quickly go through -- I won't read them, but I'll show the questions to you again. They're a set of questions that are relevant to understanding the health impact on individual smokers. There is yet another set of questions that's relevant to understanding the impact of smoking menthol cigarettes at the population level.

You've heard these before because these questions are being addressed specifically within previous chapters. But, again, this is basically what it looks like. At the individual level, we have seven questions that speak to the individual, and we'll attempt to, again, pull forward whatever conclusions or evidence that we've found into chapter 7, and it will be described here.

DR. SAMET: Mark, if you could just go back one slide.

DR. CLANTON: Absolutely.

DR. SAMET: Let me give a reminder to everybody that "access" has been changed to "availability," just as a reminder.

DR. CLANTON: Will do.

There are a set of questions that focus on public health effect at the population level. These are 1 and 2. Again, you've seen these before. And from an editorial perspective, we'll make a decision about whether we need to repeat or pull forward information about patterns of menthol use. I think it's our intention not only to answer seven questions, but also pull relevant conclusions from all of the chapters forward into chapter 7 as well.

This is a placeholder for the potential health effects of smoking menthol cigarettes. One of the issues that we're dealing with is, of course, it'll be difficult to separate smoking regular tobacco versus the health effects of smoking tobacco and menthol. But, again, these are some of the potential placeholders that we may want to address based on the evidence reviewed.

We put these also as placeholders. There is an intention to use the modeling that was previously reviewed and described once again

yesterday to bring conclusions, based on that modeling, forward into this chapter. There are placeholders here because it isn't clear whether we have the data or the time to address modeling, for example, of disease burden or chronic disease burden. But we may offer up some future research opportunities based on these placeholders, looking at health and public health impact.

This is a section that we've done a little bit of work on. And this is separate from simply pulling forward the answer to the previous questions. And I wanted to just make it clear as to why we need to address the issue of contraband.

We've been asked very specifically, as a result of the legislation and the language in the legislation, to make comments about the potential effect on contraband if, in fact, menthol cigarettes, through regulatory decisions of the FDA, are removed from the market.

This is worth reading. So if a standard were to be implemented in regard to menthol, under Section 907(b), the Secretary needs to consider

additional matters, including technical availability of a standard or achievability of a standard, and any countervailing effects on health of an adolescent and adult in non-tobacco users. Such effects could include the creation of a significant demand for contraband.

So we're being asked to explicitly address the issue of contraband.

There are three sort of overarching conceptual assumptions. First of all, we're going to have to make an assumption and also draw conclusions about a state that doesn't yet exist. Although it was very informative to take testimony and to review information related to what happens to contraband today with existing tobacco, we do want to make it very clear that we're going to have to make assumptions about a state that doesn't yet exist, and the terminology of counterfactual or counterfactual state, is that terminology applied to the process of making assumptions about a state that doesn't yet exist.

Second, at some point either as a result of

reviewing data here in this process for this report or subsequently, quantitative and qualitative estimates of the economic impact of a menthol ban will need to be assessed. Again, we'll do what we can with the evidence we have, but this may be one of those things that has to get addressed but may need to get addressed as a result of future either economic and/or research activities.

Finally, economic studies may be needed to be carried out and validated to fully assess the impact of contraband or the occurrence of contraband under a menthol ban. And this is here because we did take testimony where, in fact, one report from economists at the University of Chicago, I think, that was commissioned, brought together some estimates or calculation of what would happen under a ban.

That was not yet published. It did provide very important categories or topics that we do need to address. But in terms of actually doing a secondary analysis of that economic study or validating that study, we didn't get a chance to do

that. But, in fact, the issues are important enough to probably address that at some point.

So what we did learn is that there are two basic categories of potential activity that affect the market and availability and sale of menthol cigarettes as a result of experience from the Master Tobacco Settlement Agreement, and we did receive testimony on occurrences and events and historical learning from that process.

So the two things that actually happened, as we were told, is that not only can you get contraband-related activities, which can include production of counterfeit cigarettes, but there's another concept that was introduced called evasion. And, again, there was a nice review of evasive activities, which may not actually result in illegal activities but activities that still sort of circumvent the spirit of the law.

So we wanted to review all of those and make those were important categories to look at relative to a menthol cigarette ban. So what we did find out is that under the roll-your-own tobacco

category -- and that should be pipe tobacco; we'll correct that -- and relative to the issue of using roll-your-own vending machines, all of these capabilities represent legal, in most cases, ways of producing a product which may not be taxed at all or taxed at the prevailing rate, whether it's the excise tax, the federal excise tax or state excise tax. But we were given these as important categories to look at when it comes to evasion of the spirit, at least, of the tax law if not other elements of the law regulating tobacco.

We were given some specific examples where, as a result of some legal action on at least one manufacturer, it was possible for the manufacturer to close down and not produce cigarettes for a five-year period but, relatively shortly, return with little cigars or other forms of tobacco.

So we brought forward those examples, and we'll provide those examples here as they are relevant to the production of menthol cigars, little cigars, and also menthol roll-your-own tobacco and menthol pipe tobacco. And, again,

we'll look at evasion and the potential effect of evasion as a result of using these kind of tobacco.

We were also told a form of evasion is aftermarket mentholation. This included the purchase and use of menthol tubes and rolling paper, menthol filters, and although I'm not clear that we actually have aftermarket mentholation kits, the testimony said it might be possible that these might emerge. Menthol flavoring drops are available, and are available on the Internet today, to perform this aftermarket mentholation function, but entire kits may become available under a ban of menthol, sale of menthol cigarettes.

I do want to make a point here that we may try to explore. When it comes to aftermarket mentholation and some of these functions that are classified as evasion, I think it's going to be important to look at capacity to produce menthol cigarettes that, A, are quite similar to the level and quality of menthol cigarettes that are produced by the industry, as well as the potential to produce, in quantity, the same amount of cigarettes

in order to meet market demand.

As our economist showed us, in fact, if the production does not equilibrate or become equal to the availability of cigarettes, menthol cigarettes today, that in fact the price of black market or contraband cigarettes will rise significantly, and we do know that there is a negative price elasticity, that is, fewer people buy fewer cigarettes, as the price rises.

So the issue of capacity, we'll try to address that as best we can here, the capacity to produce cigarettes in similar quantities, in similar quality, in an aftermarket fashion.

So moving from evasion and these evasion categories we learned about, we'll go to contraband. And so what was interesting in the presentation we received is that from the perspective of contraband, it's actually easier to identify contraband menthol cigarettes, particularly if there is a national ban in effect; in other words, it's clear to law enforcement, et cetera, that there shouldn't be any menthol

cigarettes and that the fact that you can, just by smelling a package, for example, determine whether something is mentholated, that presents a very different situation for the production of contraband cigarettes, menthol cigarettes, as opposed to regular tobacco cigarettes.

We were told quite directly that it is almost impossible to identify contraband and/or counterfeit cigarettes simply by looking at them or smelling them. But menthol or mentholated cigarettes, it's actually easier to do that. So we want to include that as a category and explore that.

There won't be any revenue issues. That is, once there is a ban on menthol, basically, there's a one-time hit as it relates to the tax situation, tax revenue, whereas in the case of regular tobacco, there's sort of an ongoing loss of tobacco taxed revenue. And, again, that's a different state than exists for menthol, or would exist for menthol cigarettes.

No regulatory issues. State directories

won't be allowed to list menthol cigarettes. And, again, that comes back to the ability to do taxation through excise taxes, a different situation today for traditional tobacco versus menthol tobacco in the future. And no counterfeit issues, so there shouldn't be any menthol cigarettes under a ban, so there won't be any counterfeiting. That is, there's no competition between "legitimate" menthol brands and counterfeit brands because, in fact, all would be illegal under a uniform national ban.

There would be opportunities under contraband for masking menthol contraband. Generally, there's no reporting of cigarettes by brand, so it would make it very difficult to just -- again, in terms of a bill of lading, for example, or the examination of cigarettes coming into the country, it would be very difficult to easily look at whether something's menthol or not. So you could at least mask the packaging and identification of cigarettes coming back into the country. And there you also have the potential for

misleading packaging. All of this comes under contraband and the effect of contraband.

Likely sources of contraband, we were told about foreign manufacturers. And here I understand China is a big potential for creating and potentially importing illegally large quantities of contraband menthol cigarettes, in this case. We were told about unlicensed domestic manufacturer of menthol cigarettes, and there is unlicensed domestic production of regular cigarettes today, and there are networks associated with that.

Off-the-book manufacturing is a possibility, which is a more direct contravention of the law. And, of course, aftermarket manufacturing in the form of roll-your-own tobacco and RYO vending machines is a possibility. But here the issue of capacity is an important question to address.

Likely methods of distribution of contraband. These are the traditional ones for tobacco today. They would be the same ones that might be available to produce or bring contraband menthol cigarettes into the market, international

mail; domestic mail and couriers; Native American networks, under the title of unlicensed manufacturers; and what was described by the speaker as a white van network, simply selling cigarettes out of the back of an unidentified vehicle.

As a result -- and I'm almost there -- of some testimony that was presented, another set of important topics was identified. One, there was a quantitative estimation, at least one study that is unpublished, the effect of a black market trade. There was an economic estimation of the loss of tax revenue due to contraband.

But, again, the issue here is if there is a national ban, you get one-time hit. That tax revenue isn't going to be there any more, so you can't continue to calculate in perpetuity lost tax revenue. And finally, financial and resource implications of menthol contraband as it relates to law enforcement -- I'll add that language -- because there are resource financial issues related to monitoring importation of materials, as well as

enforcing existing laws. And this is a topic that we'll attempt to either answer as a result of existing literature, or this may end up being a research question going forward.

Organized crime has been mentioned under the category of risk of unintended consequences and youth smoking as well. There the authors felt that youth smoking actually could potentially increase because there would be no regulation, no official regulation through the law, of access to smoking cigarettes or purchase of cigarettes, say, through these alternate networks.

So I did think it was important to bring these topical areas forward. We'll see what we can do based on the evidence. But, again, where there isn't specific evidence, we will make recommendations as it relates to research opportunities.

One editorial comment about conclusions; we plan to produce a final chapter that represents the conclusions of the entire report. Chapter 7, again, is designed to pull as much of this

information about health and public health impact forward, but we're going to have to make a decision about whether chapter 7 has its own conclusions, based on that discussion, or whether those conclusions should be pulled forward into the final chapter. So that's why that's blank.

DR. SAMET: Right. Good point. And, of course, the other thing right now that we have slated to go into chapter 7, but these are all things we can revisit, would be the results of the model. And those will be important, providing some quantitative estimates for the public health impact parameters.

I think that we will probably offer our qualitative judgments on public health impact as well as whatever comes out of the model. I think they're both complimentary. I think between now and March whatever, we're obviously going to face this question. We have, I think, in chapter 7 this fairly extensive list of topics to discuss.

I think with your very thoughtful set of topics that we need to look at around the

contraband question, that in itself perhaps becomes a little bit larger than we might have been thinking, and we have had substantial input on that topic.

We will need to take a fair amount of space in our integrative answers to those questions 1 to 7 and 1 and 2. And then, of course, we have to make our recommendations, and then we'll have this overall assessment of public health impact. So maybe, as we think about this, we'll just see. I mean, I think we have the option to look at how this all best comes together in terms of the chapter.

So I'll open up both for specific questions -- you've covered a lot of territory -- and then general comments around structure and organization. And, of course, we're just simply not at the point yet of providing the integrative answers to the questions.

Neal?

DR. BENOWITZ: Two comments, and I'll start with the second one first because you talked about

contraband last. I think it's important to put a temporal perspective into it.

If you look at the example of moving from unfiltered to filtered cigarettes, at first people hated filtered cigarettes. They couldn't stand them. They thought they were terrible, horrible to smoke. But, in time, virtually everyone smokes filtered cigarettes, and there would be no black market at all for non-filtered cigarettes now, even though someone might say, well, if you make everyone smoke filtered cigarettes, there'd be a huge black market. So if there is a black market thing, it's really temporal. It'll be transient issue. I think we should make that point.

A second issue that we didn't talk about but we should, probably, in this chapter is menthol levels; what level of menthol is potentially harmful to public health? And so that's something we need to talk about at some point in time. If we think mentholated cigarettes are harmful, what's the cutoff?

DR. SAMET: Do you want to elaborate a

little bit, since you raised it, on the kinds of evidence that would answer that and whether such evidence is likely to be available?

DR. BENOWITZ: Well, as we talked about before, some estimates are at 90 --

[Brief pause.]

DR. BENOWITZ: As we've talked about before, there are some estimates that 90 percent of cigarettes contain menthol. For a lot of them, they're pretty low concentrations, below .1 percent, I think averaging .03 percent or .04 percent, something like that, for the non-menthol-characterized cigarettes.

We don't really have any data about those at all. We have tobacco company documents suggesting that they might be there to make the smoke smoother or to change the taste characteristics. We don't really have information. The only thing we have is characterizing menthol.

So I think the only thing we have data for is really to say that whatever level is like the minimal level, that it's associated with

characterizing cigarettes, we have data about that level. I don't know if other people have thoughts. not to say that lower levels might not have effects. But we don't have any data on those.

DR. SAMET: Yes. I think this is an important point around the scope of the evidence that we're looking at and what it applies to that needs to be raised here. So you're really thinking not about "level," you're thinking about this in the very qualitative way of menthol in non-menthol cigarettes versus menthol as a characterizing -- levels of menthol in cigarettes, which is the characterizing flavor.

DR. BENOWITZ: Right. But we do have data on the menthol delivery of smoke in cigarettes that are marketed as menthol cigarettes. So we do have those data.

DR. SAMET: Okay. Other comments on chapter 7? Patricia?

DR. HENDERSON: I'm not sure if this would go under chapter 7, but we were introduced to different forms of menthol that are used for the

products, including crystal, crystallated (ph) menthol, or the analogs and the different. So would that go under here, just in terms of the public health impact of the different forms?

DR. BENOWITZ: In chapter 3, we'll just mention the fact that menthol distributes throughout the pack no matter where you put the menthol in the cigarette, which would be the same as menthol crystal. And we'll mention analogs, although so far as I can tell, there are no current menthol analogs that are marketed. The reports should certainly say that if menthol is potentially harmful, that menthol analogs could also be potentially harmful. So I think we should say that.

In terms of specific health risks of menthol crystals, for example, I don't know if we have any evidence of that.

DR. SAMET: John?

DR. LAUTERBACH: Dr. Benowitz, could you particularly define what you mean by "menthol crystals"?

DR. BENOWITZ: Well, we've heard from tobacco industry documents that one way of applying menthol to cigarettes includes menthol crystals. We've heard that this is a way to evade a menthol ban. I don't really know more about menthol crystals than that. Maybe if you know more, you could tell us more.

DR. HECK: I'm not sure. I know that in terms of evading or creating self-mentholation, yes, a couple of menthol crystals in a baggie overnight can affect mentholation of the cigarettes at a level similar to that seen in commercial production. And certainly the mechanisms of addition of menthol vary among manufacturers. Some manufacturers add it to like packaging materials, let's say, and it's partitioned into the product. Others spray it on in an alcohol solution. It can be added to the filter.

But I think in terms of legitimate production, all of those different application routes would be for the express intent to provide the characterizing flavor.

Does that help?

DR. LAUTERBACH: Well, what I just want to get across is that generally people don't do commercial mentholation using menthol crystals before they're dissolved in a medium or melted and put into certain applicators you can put on cigarette filters. This is why I got confused about the term menthol crystals, like people were putting menthol crystals in their cigarette.

DR. HECK: Some individuals may do that now. I don't know.

DR. SAMET: The super high menthol.

Dorothy?

DR. HATSUKAMI: Mark, are you going to be writing about ways to mitigate any negative consequences associated with the issues that you have brought up, as well as potential? If a conclusion might -- we might arrive with a conclusion that there may be a ban, what are some ways to make sure -- or should be a ban, ways to make sure that the public health is protected?

DR. CLANTON: Dorothy, I think that's a good

point. So what you're suggesting isn't there and should be, which is we need to address issues related to cessation services, for example. If in fact there is a ban and there is a hyper demand for cessation services in the report, I certainly need to add something related to what we would expect might be needed in terms of increasing cessation and counseling services. There may be some additional points to that, but it's not there. And we'll certainly bring that forward.

DR. SAMET: I think probably this kind of discussion is a little bit preliminary, given where we are. I mean, certainly the focus of our recommendations will relate to the presence of menthol cigarettes as to whatever policy measures might or might not take place.

Subsequently, I think we can maybe point to issues, and, certainly, we'll be spending time on the contraband issue. But I don't think we'll be -- in terms of where we draw the line, we might point to this substantial problem. I don't think we'd necessarily point to the steps that are taken

to address it. That's certainly, I think, outside the scope of our expertise.

Mark?

DR. CLANTON: But it wouldn't be -- I understand your point. We would need to get into a comprehensive discussion of what might be needed to address public health and medical needs. But maybe a mention or two might suffice just to say, here are some of the things you need to think about.

DR. SAMET: Let's see. Other questions or comments about chapter 7?

Melanie, if you're still there, do you want to say anything?

DR. WAKEFIELD: I am still here. Can you hear me?

DR. SAMET: Yes.

DR. WAKEFIELD: I suppose I've just been thinking about the tobacco industry response in terms of product alternative brands. I mean, we've just seen a Newport Red come onto the market last year. I guess that potentially could be conceived to be positioned to capture -- to try to capture

any Newport menthol smokers in the event of a ban, if there were to be one.

So I'm just thinking there should be some consideration given to other product labeling or branding that smokers might think share some similarities with menthol cigarettes, whether it's in the brand name or whether it's in what the brand might promise, which might cause people to simply switch from -- be more likely to switch from menthol to non-menthol rather than potentially quit.

DR. SAMET: Okay. Thank you.

Anything else?

[No response.]

DR. SAMET: Okay. We will have a chapter 8, but there's nothing to discuss yet.

I'd asked Dan about providing us with, I think, an informal overview. And I think, given the hour, why don't we go ahead and do that without a break. And thank you for doing this on short notice.

Industry Perspective

DR. HECK: Yes. Thank you, Mr. Chairman.

The FDA had asked the industry to provide an industry perspective on this topic. We are working on assembling that perspective or report. We have a number of draft chapters, an introduction. The chapter topics are similar to, not identical to, those that the voting members have outlined here.

I think the industry perspective will probably be narrowly focused as much as possible on the explicit charge to the committee from the FDA, which has been shown several times today here.

With regard to the -- I think the toxicology, epidemiology, biomarkers chapters will be quite similar to those of the voting members report.

With regard to the behavioral studies, the survey studies in the most part, we've seen from some of the presentations over the course of this deliberation, that those types of studies, the behavioral studies, the NSDUH and others, are subject to different interpretations by different parties, depending on their perspectives, and those

different interpretations may be valid.

I think it seems, to the difficulty we have, we're asked basically to kind of develop a causal inference with regard to menthol and causing behaviors. And as we all know, doing that from survey or cross-sectional type data is a difficult process. That said, this type of data is the majority of the information we have on this topic. So I think we're all forced to look at and examine what data we have to try to develop our respective opinions.

On the marketing topic, I think there'll be -- we've seen some presentations of contemporary marketing practices in July and elsewhere in this process. I anticipate that the industry's report will be less interested in the historical and prehistorical marketing and advertising and issues that have been of some interest to some members of the committee, and former members.

I think that in terms of FDA's purview and regulatory authority over tobacco products, its contemporary practices and practices going forward

that are most relevant to FDA -- and I think the industry's report will intend to address FDA's needs and concerns going forward, in the main.

I think Mark did a pretty thorough job of outlining the countervailing effects. We've seen presentations on that topic the last several meetings. I think that the commentary on that will be drawn, in the main, from some of the submissions that have been made to date by the industry. I don't think we'll be writing – and, in fact, throughout this report, I think there'll be an effort to draw a balance between incorporating by reference prior commentary and submissions as opposed to rewriting the book, rephrasing the book again.

I think pulling all the information together in a comprehensive manner will be most useful to FDA in their own deliberations subsequent to this committee. But we'll try to draw a balance between that and unnecessarily duplicative recitation of things that have already been submitted or provided for the record.

So progress is underway and being made on that, and we fully expect to be able to provide that report on or before the date specified in the statute.

DR. SAMET: Just to return to a little bit of our conversation yesterday about timing, and we're all at the mercy of the -- not at the mercy, we're all answering to the same difficult deadline. And to the extent that your report and summary and synthesis would be of value as the Menthol Subcommittee writes its report, there would need to be some opportunity to take a look, possibly before the early March meeting.

We are anticipating -- I think we're going to talk a little bit about some of the schedule issues -- but we're certainly anticipating having drafts completed of the various chapters, probably with the exception of some of chapter 7. So I think if you feel that it would be helpful for us to look at the report that you're taking the lead on, we want you to have a sense of the time here.

DR. HECK: I think that's one of the

unfortunate aspects of the exclusion of the industry representatives from the main report-writing process. We have to -- we are diverse industry with some diverse perspectives on the approach in some of these areas. And we have to -- to the extent this will be a consensus report, there may be other submissions in addition to this report. I mean, some may choose to comment on the topic separately from this report.

Certainly, we'll provide an opportunity for all who may be interested to review, approve, sign onto this consensus effort. So we have that additional step built in, but our intention certainly would be to get the report completed and made available as soon as possible. I know that's not a specific date.

DR. SAMET: There's a couple of issues that I want to follow up on, but one that maybe, Corinne, this goes to you.

Was there an expectation there would only be a single industry report coming via our TPSAC industry representatives?

DR. HUSTEN: Yes. I believe that was our expectation, although, obviously people -- anyone can submit under the open public hearing and the public comments. So there's an opportunity for those other types of perspectives. But we had envisioned an industry perspective document.

DR. HECK: Yes. I just wanted to accommodate -- I'm not in daily contact with all the diverse elements of the industry and their thinking on even a sub-topic. Some may be more interested in some of the topics than others and may wish to, as you say, through the open public process, provide additional or alternate commentary. And I want to just acknowledge that that reality is there.

DR. SAMET: Well, let me ask a related question since you and John and Arnold represent different aspects of the tobacco industry. Will this report be coming from the manufacturers with you as the representative, or is it coming from the three sectors that you represent? And I guess that sort of relates to, will it come with designated

authors and that kind of thing, or do you know yet? Perhaps you may not know.

DR. HECK: I guess I don't know. I've seen my own role as more of a coordinator/editor, if you will, although I certainly wouldn't exert editorial prerogative over someone else's strongly held opinions or interpretation. And if that can be accommodated in a single report, I think the diverse opinions of the industry are welcome.

But I just don't know with certainty which company or companies may choose in the end to sign onto this opinion report. But it'll certainly be as inclusive and representative of the industry as a whole as I or we can make it.

DR. SAMET: And John or Arnold, do you want to comment? You don't have to, but if you -- okay.

So actually, I think we did get stalled on the timetable issue. I'm not sure we ever -- I expressed the TPSAC -- the Menthol Subcommittee's timetable and when we would probably need to perhaps see drafts. And I think, Dan, you then got into the complexities of developing a report.

Believe me, I understand those -- well, to some extent. But could you come back, then, to whether you think there is a timetable in your development of the drafts where we could take a look at them?

DR. HECK: I will have to consult with all the fairly active participants here, but the March time frame, as opposed to the next week time frame, seems realistic, with the additional promise that as soon as possible, this will be done. I expect to be cloistering myself the next week or two to try to get the final revisions and consolidation complete for circulation among the industry parties.

DR. SAMET: Okay. Thank you.

Other questions from the group? Patricia?

DR. HENDERSON: I just have a question about the process. Is this report recommended by Congress, the industry's report?

DR. SAMET: Corinne?

DR. HUSTEN: Congress has just asked the TPSAC to develop a report. We had asked, since we

thought there might be varying perspectives on the various issues, for the industry to provide an industry perspective document.

DR. HENDERSON: And how much will that be weighted in, I guess, the final decision?

DR. HUSTEN: Well, I mean, as we are thinking about the issue of menthol, we will be looking at any and all information that came to the committee, the committee's recommendations, other scientific evidence that we may have available or that become available, such as some of the industry documents where we don't have the reports yet, and things like that. So we'll be taking into account, certainly, the committee's report as well as other scientific information.

DR. SAMET: Melanie, any questions? Melanie, just to check, do you have any questions here?

DR. WAKEFIELD: No. I don't have any other comments.

DR. SAMET: Thank you.

So, Dan, anything else on this?

DR. HECK: No. No, I don't think so.

Committee Discussion

DR. SAMET: Good luck.

Okay. Let's see. I think there's a few other things that I would like to just touch on. And, actually, while we're at some of the structural issues, the report itself would be – and, Corinne, this is just something we might think about -- presumably this would be characterized as developed by the Menthol Subcommittee of TPSAC, and then, I guess, reviewed and approved by TPSAC. And do we in the end, some wonderful day in March, we're sitting here voting yes, accept, or no, reject, or something?

DR. HUSTEN: Well, the report has to come to FDA from the TPSAC. And generally how it works with subcommittees and committees is that the subcommittees report to the full committee in whatever way you deem most useful, whether that's presentations, drafts, or the subcommittee's final draft.

But then the full committee needs to look at

it, discuss it, provide any comments. And then if there are changes that need to be made based on those comments, then as members of the TPSAC, there won't be another -- we'll have to think through how the subcommittees formally report in. But, again, it can be presentations or the drafts. But it's the TPSAC that has to decide what the final report is and transmit it to FDA.

Did that make sense or confuse it more?

DR. SAMET: Both. It seems to me, obviously, the anomaly here is that we are -- the subcommittee is the TPSAC minus one at the moment, and then we have some special government employees, at least one who has weighted in, in an important way, helping to develop the draft.

I think it would be useful to have a pretty clear understanding of what we do. I think what it sounds like is that when we have a final report, it is discussed at a full TPSAC meeting, and presumably needs -- actually, will we need to vote to accept it?

DR. HUSTEN: Well, and whether it's a vote

or not, certainly there has to be -- the committee has to submit the report; so whether it's a formal vote or there's just a discussion and agreement that this is the report that will be submitted, but the report does have to come from the full committee, not from the subcommittee. And so there does need to be a discussion in a full TPSAC meeting of the report, certainly the conclusions and the recommendations.

DR. SAMET: Okay. Yes, Dan?

DR. HECK: Just a small comment, maybe in advance. Should closing of our deliberations here in the next couple meetings entail votes, we might need a legal opinion. I'm not an expert on the Advisory Committees Act, but my reading of that suggests that non-voting members do have the privilege of voting on procedural matters, not on, I guess, committee decision matters or whatever.

So should there be some procedural-type votes, it's my understanding that the industry reps and other non-voting members do have a vote in that circumstance. But, again, I'm not an attorney in

that area.

DR. SAMET: We just happen to have an attorney here.

DR. TEMPLETON-SOMERS: Oh, I'm not an attorney.

DR. SAMET: Oh, you're not?

DR. TEMPLETON-SOMERS: I think we may have one over there, though. But generally, by "procedural matters," they mean things like, are we ready for lunch? And so I'll check with the attorneys to make sure of the scope of that, but I doubt if it would be a scientific recommendation.

DR. SAMET: Well, I will say that I'm not sure I anticipate any procedural matters, but we will keep that in mind. And I think, as you've seen from our chapters 1 and 2, one of the principles that we have adopted is that as we develop recommendations and reports, it's going to be consensus-based from both the Menthol Subcommittee and the TPSAC.

So I don't see, as a group, just to make this clear, that there would be, for example,

committee votes on level of evidence or that kind of thing. This will be written, and these will be consensus-based recommendations coming from the subcommittee to the committee.

Okay. Other things? So I think we have some sense, then, of the time frame. Early March meeting, as I have said, it's unfortunate that February lacks three days because we could have all used them. But this will just help us get to the end of our task more quickly.

At the meeting in early March, we would anticipate having the draft chapters up through 6 posted and available for review and discussion by the -- review by the public. Remember, however, that for new information that is to be brought to our attention, written submissions, they need to be in by February 15th.

Subsequent to this meeting, I would say that we would certainly have our answers to the seven and two questions and be working on the draft recommendations; and, presumably, receive that final discussion and, if you will, transmission

to TPSAC at the March, I guess, 17th meeting. So that's the time frame. So we all have a roughly impossible month or so ahead of us.

So let me ask if there's anything else that anyone would like to bring up now. Yes, Dorothy?

DR. HATSUKAMI: Jon, it would be nice if chapter 5, at least, had a little bit more time than the early March deadline, just because we're trying to integrate all the marketing with what we have.

DR. SAMET: Right. So chapter 5, which will certainly be the lengthiest, will probably need some extra time. So probably that final draft for discussion and posting will probably come after the March meeting, and then completed and finalized, as I discussed, at the mid-March meeting.

Adjournment

DR. SAMET: So before we adjourn -- I assume we don't need a procedural vote on adjournment. But if there's anything else, this is the time. Again, I want to thank everybody for a tremendous amount of work to now. We've certainly had very

useful input from the public and many stakeholders who have provided us with information along the way.

Caryn, any last words? No? Okay. Thank you, then. We are adjourned.

[Whereupon, at 11:23 a.m., the meeting was adjourned.]